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By Linda Burgess

PATENT

Atty. Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS

In re application of:

Richard H. Tullis

Serial No.: 08/078,768

Filed: June 16, 1993

For: OLIGONUCLEOTIDE THERAPEUTIC AGENT AND METHODS OF MAKING SAME

Examiner: J. Martinell

Art Unit 1804

APPEAL BRIEF

Commissioner of Patents
Washington, D.C. 20231

Sir:

The following is appellant's Brief submitted in triplicate pursuant to 37 C.F.R. 1192(a).

Please deduct the requisite fee, pursuant to 37 C.F.R. §1.17(f), of $280/290 from deposit account 20-1430 and any additional fees associated with this Brief.

TABLE OF CONTENTS

I. STATUS OF THE CLAIMS

Claims 64-72 are pending in the applications. All of the pending claims are being appealed and are set forth on the attached Appendix.

II. STATUS OF AMENDMENTS

No claims have been amended after the final office action was mailed on November 28, 1994.

III. SUMMARY OF THE INVENTION

This invention is a novel method for selectively controlling the expression of protein in a living cell. The method involves exposing cells to nucleic acid that selectively binds to the coding region of messenger RNA and prevents it from being translated into protein. Under normal circumstances, cells make or express hundreds of different proteins at any given time. Cells make protein by transcribing their genomic DNA into messenger RNA (mRNA). The mRNA then travels from the cell nucleus to the protein making apparatus of the cytosol. This apparatus, which includes ribosomes and other subcellular components, reads the coding region of the mRNA and expresses a specific protein.

The coding region of a mRNA comprises a nucleotide base sequence that mirrors the sequence of the genomic DNA. The order of the nucleotide sequence is analogous to the order of the words of a sentence. The order of the nucleotide sequence is as specific for a particular protein as the order of words are to the particular meaning of a sentence.

The inventive aspect of this work is the discovery that nucleic acid will bind to the protein coding region of the mRNA and that if the binding nucleic acid is of sufficient length, translation of the protein by ribosomes can be halted. Previously, workers had thought that these coding regions were unavailable for binding by nucleic acids because of extensive secondary structure. The prior art confined their work to the "open" regions of the mRNA. Because the base sequence of

mRNA coding regions are very specific for each protein, this invention provides a degree of selective control over protein expression that was previously unavailable to workers.

IV. ISSUES

The Board is asked to review a single rejection under §112, first paragraph. The rejection is maintained for multiple reasons, all of which are legally insufficient to support the rejection. The pending claims read on natural and stabilized nucleic acid. They are rejected as not enabled beyond a single modified nucleic acid, i.e., a phosphotriester analog of nucleic acid. The following statement of the issues is offered to the Board:

1. Can the examiner continue to reject claim 71, limited to stabilized nucleic acid, as non-enabled where the appellant has provided declaratory evidence from two experts who set forth three objective reasons why those of skill in the art would have readily understood from the specification's teaching of a general class of stabilized nucleic acid and of a single example that the appellant was intending to claim a small class of well known stabilized nucleic acid analogs and where the examiner has not provided any reasons why the declarants' three objective reasons are incorrect or inadequate?

2. Can an Examiner reject claim 71 as non-enabled because he believes, without objective reasons, that those of skill might have to conduct a literature search to identify other members of the family of stabilized nucleic acid and in view of the fact that the family was summarized in the literature by a routineer three years before the filing date of the parent application?

3. If an examiner raises colorable arguments regarding the ability of cells to internalize stabilized nucleic acid and the ability of stabilized nucleic acid to

bind to mRNA by complementary hybridization, can the examiner properly maintain his §112 rejection without objective reasons or without citation to published references where appellant rebuts the two arguments with objective reasons through declaratory evidence and with citation to prior art references that directly contradict the examiner's understandings?

4. Where an applicant states that both stabilized nucleic acid and natural nucleic acid will function in his invention and where the examiner challenges this statement of utility under §112, can the applicant properly submit later state of the art references to prove that his allegations of utility were true?

5. If claims are directed to the binding of the coding region of mRNA with nucleic acid and the inventive principle is the discovery that the coding region of mRNA is available for binding by nucleic acid, is the claim properly rejected as nonenabled where the specification recites natural nucleic acid, expresses a preference for stabilized nucleic acid and provides an example of stabilized nucleic acid?

6. If claims are directed to the binding of the coding region of mRNA with nucleic acid and the inventive principle is the discovery that the mRNA is available for binding, is the claim properly rejected because under some conditions but not all, stabilized nucleic acid might work better than natural nucleic acid?

V. GROUPING OF THE CLAIMS

Claims 64-72 are rejected under 35 U.S.C. §112, first paragraph. The claims **do not** stand together. The Examiner has articulated multiple grounds for rejection of the claims when inclusive of natural nucleic acids. However claim 71 is directed to nuclease resistant nucleic acid and thus stands apart from the other

claims because not all the grounds for rejection of the broader claims are applicable to claim 71. Thus the Board may find claim 71 patentable while not agreeing that the other claims are patentable.

VI. ARGUMENT

The Examiner has raised multiple bases for supporting his §112 rejection. This Brief is divided into seven subsections. Each subsection addresses a separate basis raised by the Examiner to support the single §112 rejection. Because claim 71 would be patentable if not for a single issue, appellant addresses this issue first.

With regard to claim 71, the issue is simply whether the specification, as filed in 1981, provided adequate instruction for those of skill, to identify other stabilized nucleic acids which were available in 1981. Appellant rebuts this legal conclusion in section 1, first by urging that the *prima facie* case of non-enablement has not been properly supported by objective reasons and second by presenting two declarations by persons of skill in the relevant art in 1981 in which three separate and objective reasons are provided to explain why the specification enables the claim.

In section 2, appellant addresses the Examiner's concern regarding which nucleic acid to use and how to use the nucleic acids. In response, appellant explains that any nucleic acid would work: both natural and stabilized, and that they are all used in the same way as the exemplified analog which is the subject of a related U.S. patent.

In sections 3 and 4, appellant addresses two colorable concerns regarding the ability of cells to internalize stabilized nucleic acid and the ability of stabilized nucleic acid to bind to mRNA by complementary hybridization. Appellant cites to published reports describing internalization of modified nucleic acid and relies on two experts who in their Rule 132 declarations attest: (1) that cells generally have a ready capacity to internalize small oligonucleotides of the types taught by the

specification. Appellant then cites to multiple published reports disclosing the ability of stabilized nucleic acid to bind to complementary nucleic acid and explains that stabilized nucleic acids are designed by chemists to be analogs of nucleic acid. They are designed to bind via complementary bases in a manner analogous to natural nucleic acids - otherwise they would be biologically useless.

In section 5, appellant addresses the Examiner's concerns over stability of natural nucleic acid. It is acknowledged that nucleases exist in the external and internal cellular environments. Nucleases are enzymes that can degrade nucleic acids and prevent them from binding to mRNA. This well recognized fact gives justification to the appellant's preference for nucleic acids that are stabilized against degradation. However, the Examiner has unduly focused on appellant's preferred embodiment to support his opinion that the natural nucleic acids are inoperable. In response, appellant argues: (1) that this rejection is a hybrid §101/112 claim and should be held to the classic standards articulated by this Board and courts as to utility; (2) that there is no reason to believe that natural nucleic acids would not work if you simply used enough to overwhelm the enzymes present; and, (3) that post filing date references fully support the stated utility for natural nucleic acid.

In section 6, appellant briefly addresses the enablement rejection under a pure undue experimentation analysis relying on statements by the two experts. Although the Examiner has not specifically raised any concerns regarding the "how to use" prong of §112 except in the confines of which nucleic acid to use, appellant would be remiss if he did not explain to the Board that practice of the invention is trivial once the inventive aspect of the claims is taught.

In section 7, appellant explains that the inventive aspect of this invention is the choice of target (i.e., mRNA coding region) and not the choice of nucleic acids for binding to the mRNA. The Examiner's rejection is based on his belief that the specification fails to adequately identify the world of nucleic acid analogs which would function in the invention. In contrast, appellant viewed in 1981 and still

views this aspect of the work as a trivial and non-inventive feature of the invention. Section 7 summarizes decisional law in which the CCPA has expressly mandated that enablement issues should be focused primarily on the inventive aspects of the claims and that restricting patent claims to non-inventive aspects will result in unfairly limiting the claims.

1. ONE OF SKILL WOULD UNDERSTAND THAT THE SPECIFICATION WHEN REFERRING TO STABILIZED NUCLEIC ACID WAS REFERRING TO A SMALL CLASS OF WELL KNOWN NUCLEIC ACID ANALOGS.

As filed, the specification teaches that both modified and unprotected nucleic acid can be used in the invention. The modified nucleic acid is exemplifi d by a phosphotriester analog. The specification at page 4, lines 9-13, illustrates this teaching:

> The preferred oligonucleotide has a minimum of about fourteen or more bases, such as about twenty-three bases, and for increased stability, may be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation during use.

The original claims track this teaching. According to claim 1, the compositions of this invention are oligonucleotides. In the dependent claims, the inventor claims oligonucleotides that are preferably transformed into a more "stable form to inhibit degradation" by the host organism (claims 2, 29, 40, 45 and 49) and are preferably a "phosphotriester form" (claims 3 and 30). In summary, the specification generally suggests the use of both natural and stabilized, nucleas resistant oligonucleotides and provides a single example of stabilized nucleic acid.

The Examiner has urged that the specification, as filed, fails to teach one of skill which stabilized oligonucleotides are useful in the invention.

In the Advisory Action mailed May 4, 1995 (Paper No. 35) the Examiner clarified his remaining basis for rejection of the pending claims which included claim 71. He states:

> Reference to the Office Action mailed December 16, 1992 reveals the actual issue, which is that the instant application fails to guide those of skill in the art as to which oligodeoxyribonucleotides to use.

The Examiner continues by arguing that the appellant's Response filed on April 17, 1995, was "most unconvincing" because it merely explained that the oligonucleotides existed and failed to show "how to use them" and "fails to even mention the different forms of oligodeoxyribonucleotides in any specific manner."

He states in his Advisory Action mailed on August 21, 1995 (paper No. 40):

> However it cannot be agreed that the scant statements in the application (e.g., at page 4) in regard to the use of stabilized forms of oligonucleotides are in any way adequate direction for those of skill in the art as is required under the statute.

Thus it would appear that the Examiner's concern over the modified nucleic acid is not that they would work but that the specification merely failed to adequately identify them. In response, appellant explains in subsection A that the Examiner's position is not legally sufficient for failure to state objective reasons in support of his legal conclusion and in subsection B, appellant presents objective reasons rebutting the legal conclusion.

A. The Examiner's reasoning is not sufficient to support the *prima facie* case of non-enablement.

Appellant acknowledges that it is entirely proper for the Examiner to question the adequacy of a disclosure and if the Examiner has objective reasons to support his concerns, patent applicants are required to present objective evidence to rebut the examiner's position. *Application of Angstadt*, 537 F.2d 498 (CCPA). In *Angstadt*, 537 F.2d at 504, the CCPA, stated:

> We note that the PTO has the burden of giving reasons, supported by the record as a whole, why the specification is not enabling.

The Examiner's burden of proof for setting forth an initial rejection is low. It is by a preponderance of the evidence. *In re Caveney*, 226 USPQ 1 at 3, (Fed Cir 1985). While the standard is low, the evidentiary burden cannot be satisfied by conclusory statements that a claim is not enabled. This Board has more than once reminded an examiner that a *prima facie* case of enablement must be supported by objective reasons. *See, e.g., Ex parte Hitzeman*, 9 USPQ 2d 1882 (PTOBPA&I 1988). In *Hitzeman*, the Board termed legally sufficient, objective reasons as "sound scientific reasons".

In contrast to the Board's mandate, the Examiner maintains this part of his rejection based upon a naked opinion unsupported by objective reasons. The Examiner has repeatedly stated that the specification fails to direct those of skill to alternative stabilized oligonucleotides and that recitation of a single example of the group is inadequate support. However, he fails to provide sound scientific reasons as to why he believes skilled persons would undertake undue experimentation to identify alternative forms of stabilized nucleic acid. Although he may sincerely believe that those of skill *should not* have to be "expected to do literature searches and be led from one researcher to another" (Paper No. 40), he does not state **sound scientific** reasons why he believes that those of skill in nucleic acid/protein expression arts in 1981 would not already be aware of this art nor does he explain why a need for a literature search, for those who are unaware, would lead to a conclusion of undue experimentation under §112.

Simply stated, the Examiner cannot maintain this rejection because he was personally unaware that alternative analogs were known in the art. This is especially true in view of the statements of Drs. Schwartz and Ruth as to what was known in the art in 1981.

The Examiner could have argued that the art is particularly complex or unpredictable and that undue experimentation would be required to enable one of skill in the art to practice the invention. He has not so argued. As in *re Goff*, 191 USPQ 429, (CCPA 1976), there is in this case only naked assertions. There is no objective reasoning to support the Examiner's opinion that those of skill in 1981 would not recognize, without complex or unpredictable investigation, a variety of other stabilized nucleic acids for use in this invention even after express exemplification by phosphotriester analogs.

Finally, the selection of the stabilized nucleic acid was not considered a special focus of the invention. Any stabilized nucleic acid works. While stabilized nucleic acids are important, they are an ancillary part of the invention *per se*. Under some circumstances, enzyme activity might degrade natural nucleic acid and

the appellant suggested using modified nucleic acid that was known to be stable under such conditions. *The actual invention was the discovery that the coding region of the mRNA was a suitable target for binding and that given an appropriate length, the nucleic acid could bind and prevent translation of protein.*

The record before the Board clearly evidences that both natural and stabilized nucleic acid work in the invention. There are three published references in the record and affirming Rule 132 declarations of Drs. Schwartz and Ruth that attest to the operability of natural nucleic acid. Because both natural and stabilized nucleic acids function to downregulate protein expression, appellant urges that the Examiner's concerns regarding a need to specify a variety of specific stabilized nucleic acids is legally unnecessary. Analogs were not then and are not now the focus of the invention; rather, they are merely a preferred and conventional alternative of one element in the invention.

B. The record specifically provides three objective reasons why one of skill would not have undertaken undue experimentation to identify other stabilized nucleic acids, in addition to phosphotriester modified nucleic acids.

Presuming for arguments sake that the PTO has met its initial burden and a reasonable doubt regarding enablement is raised, the *prima facie* case of non-enablement is still rebuttable. *Ex parte Hitzeman*, 9 USPQ 2d 1882 (PTOBPA&I 1988). Accordingly, a patent applicant need not rebut a *prima facie* case of non-enablement, of utility or of obviousness, by overwhelming the Examiner with evidence. The proper standard for rebuttal is simply to place the issue into equipoise. *In re Oetiker*, 24 USPQ 1443 1992.

Given that the above evidentiary framework is the accepted framework for the way we establish conclusions of law and by extension is the hallmark of the patent examination process, appellant has initially argued, above in subsection A, that the *prima facie* case of nonenablement is not adequately set forth. In this subsection, appellant presents objective evidence that, at a minimum, places the status of the various issues into equipoise if not overwhelmingly in favor of

patentability. Nothing more is required of a patent applicant and absent any good reason to doubt the opinions of the experts in their Rule 132 declarations, the matter must end with the rejection being withdrawn. *In re Soni*, 34 USPQ 1684, 1688 (Fed Cir 1995).

With regard to claim 71 specifically and the remaining pending claims in general, the question is whether the specification adequately directs the skilled reader to alternative, modified oligonucleotides without specifically identifying other members of the class. In response to the Examiner's concern regarding difficulties those of skill in 1981 might have had identifying other stabilized nucleic acid, appellant has submitted Rule 132 declarations from two nucleic acid experts. Both experts were conducting related nucleic acid research in 1981. Both experts gave objective reasons why they believe that they and others of equal skill would have been readily able to conceptualize and to identify other members of the group of stabilized nucleic acid from the teachings of the application, i.e. a general description and specific example.

The declarants have made specific reference to the specification at page 4, lines 9-13 which states:

> The preferred oligonucleotide has a minimum of about fourteen or more bases, such as about twenty-three bases, and for increased stability, may be transformed to a more stable form, such as a phosphotriester form, to inhibit degradation during use.

In section (A)(1) of the two declarations filed on April 14, 1995, each declarant identified five academic references which are representative of the state of the art in 1981 with regard to nuclease resistant oligonucleotides. The Examiner has agreed in paper 35, page 1, section (a) that members of the group of stabilized nucleic acid were known to exist; but, he still insists that it would require undue experimentation to identify those members.

In section (A)(2) of their declarations, the declarants provided multiple objective reasons why they, as persons of skill in 1981, would have understood

1804

PATENT

Attorney Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS

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In re application of:	
Richard H. Tullis	Examiner: J. Martinell
Serial No.: 08/078,768	Art Unit: 1804
Filed: June 16, 1993	COMMUNICATION PURSUANT TO RULE 1.192(c)
For: OLIGONUCLEOTIDE THERAPEUTIC AGENT AND METHODS OF MAKING SAME	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed are three copies of the SUBSTITUTE APPEAL BRIEF with the appropriate substitute page iii inserted accordingly.

No fee is thought necessary as the Examiner has indicated a period of one month until February 19, 1996, to comply with Rule 1.192. However, if a fee is required, the Commissioner is authorized to charge Deposit Account No. 20-1430 any fees appropriate to this Communication.

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Respectfully submitted,

Kenneth A. Weber
Reg. No. 31,677

Dated: February 2, 1996

the specification to be referring to a specific body of knowledge relating to nuclease resistant nucleic acids. Their objective reasons are as follows.

(1) There was no body of knowledge relating to nuclease resistant nucleic acid which would *not* function in the invention and would confuse those of skill. Thus if one of skill knew of or identified stabilized nucleic acids, they are all equivalents for use in the invention. There was no unpredictability or complex selection process to consider.

(2) There was a general teaching in the specification to nuclease resistant nucleic acids with an example to a phosphotriester modified nucleic acid. This specific reference would have guided even an undergraduate student to Dr. P.S. Miller's work. According to the declarants, this was sufficient teaching to suggest all of Miller's related work on modified nucleic acids which included phosphonate analogs. Furthermore, there was a second well known scientist working in this field and according to the declarants anyone of skill familiar with Miller's work would also have known about Dr. F. Eckstein's work with nucleic acids modified to resist degradation.

(3) The declarants further aver that the level of skill in the scientific community in 1981 was such that routineers had the ability to conduct literature surveys. In accord with this fact was the discussion by Summerton in reference A28. The Summerton article was published in 1978 and expressly summarized the relevant body of knowledge concerning stabilized oligonucleotides on page 89. How can the Examiner maintain his position regarding undue experimentation over which stabilized oligonucleotides to use, when Summerton had summarized the field in 1978? This was three years before the effective filing date of the instant application.

Based upon the above objective facts, the declarants concluded with their opinion that they would have understood the specification to refer to the various modified nuclease resistant nucleic acid analogs available in 1981.

The Examiner has not adequately responded to these objective statements by the declarants. These three rebuttal points were most recently raised as points 1 and 2 in appellant's paper submitted on July 20, 1995. In response, the Examiner wrote in paper No. 40:

> Indeed, applicant's strenuous argumentation to the effect that those of skill in the art would be expected to do literature searches and would be led from the work of one researcher to another and would see that work on a background of hypothetical information that is only speculated at (e.g., see points 3, 4, and 5 on page 5 of the Response filed on July 20, 1995) all support the notion that the specification does not teach those of skill in the art how to make and use the invention.

Therein is the sum total of the Examiner's "objective reasons." Each reason begins with the word "would."

The Examiner apparently believes that those of skill (1) **would not** be expected to do literature searches, (2) **would not** be able to identify other people's work from that of the exemplified species, i.e. Miller to Eckstein to the Summerton summary and (3) **would not** "see that work on a background of hypothetical information that is only speculated at . . ."

In response, appellant addresses the first two reasons by relying on the statements of the experts. In particular, appellant again states that the selection of the modified nucleic acid is a routine aspect and is not an inventive aspect of the invention. There is no evidence in the record to the contrary and patent applicants need not teach what is already known in the art. As the CCPA stated in In re Folkers et al., 145 USPQ 390, 394 (1965):

> Yet we also recognize that patent disclosures are not necessarily required to be meaningful and intelligible to the general public. They need not set forth minutiae of description or procedures perfectly obvious to one of ordinary skill in the art yet unfamiliar to laymen. As this court stated in In re Chilowsky, 43 CCPA 775, 222 F.2d 457, 108 USPQ 321, 324.

See also *In re Gay*, 135 USPQ 311 at 314, (CCPA 1962) which states that patent specifications are directed to those of skill and not to the general public.

Surely if the appellant's invention of downregulating protein expression had been known using unmodified nucleic acid, the use of stabilized nucleic acid would

have been an obvious variation and unpatentable under §103. The declarants have stated that those of skill would have either known about the analogs or would have able to locate the analogs using a conventional literature search. Although the Examiner impliedly questions the truth of the expert's statements, he has not identified any objective reasons for this Board to doubt the veracity of the statements by the declarants nor of their ultimate conclusions. Thus their expert opinions are based upon uncontroverted objective reasons and this classically leads to the conclusion that the specification comports with the requirements of §112 .

With regard to the third reason articulated by the Examiner, it is a poorly constructed clause and appellant requests clarification in the Examiner's Answer.

In view of the above facts, the appellant believes that the Board should reverse the Examiner on this first basis for maintaining the rejection of claims 64-70 and 72 and reverse entirely the rejection as to claim 71.

2. THE SPECIFICATION ADEQUATELY TEACHES THOSE OF SKILL WHICH OLIGONUCLEOTIDES TO USE AND HOW TO USE THEM TO DOWNREGULATE SPECIFIC PROTEINS.

Having explained above that the identification of alternative analogs was within the grasp of the routineer, appellant addresses here issues regarding which analogs work and how to use them. In the Examiner's comments on May 4, 1995, he states:

> the applicant's arguments ... are most unconvincing in the absence of a mention or teaching in the application as to how to use them [oligonucleotides].

It is not entirely clear that the Examiner still considers this point to be at issue or whether the Examiner was actually concerned about undue experimentation required to identify alternate forms of stabilized nucleic acid. Nonetheless, appellant offers three responses to the above concern.

First, appellant will presume that the Examiner has a real concern regarding how to use the nucleic acids. If the Examiner is actually concerned about *how* to use the modified nucleic acids rather than *which* nucleic acids to use, the Board is reminded that the teachings of this specification were considered adequate by the

same Examiner for the issuance of the related U.S. Patent No. 5,023,243 ['243]. If this very same specification was deemed adequate to enable one of skill to use the phosphotriester analogs to control protein expression, then this instant continuation should be adequate for the pending claims, once the Examiner is persuaded that the requirements of §112 are otherwise satisfied.

The appellant has previously stated for the record that the methods for using the different stabilized oligonucleotides are essentially identical to the methods for using the unprotected and the phosphothioester forms of nucleic acids. Physical use is trivial. One simply floods the external environment of the target cells with sufficient amounts of nucleic acid until downregulation of the target protein is obtained. The key to using the invention is in the use of a specific length oligonucleotide, not in how you physically expose it to the cells. Other than the Examiner's stated concerns over hybridization and internalization of stabilized nucleic acid, there is no objective evidence in the record to the contrary, no evidence of unpredictability, and no evidence of undue complexities.

Secondly, Drs. Schwartz and Ruth in Section D of their declarations filed on April 14, describe in detail why there is no undue experimentation in simply bathing target cells with the degradation resistant nucleic acid. The experts both stated:

> The level of skill of those in the art of antisense technology is quite high. Most of the artisans are like myself and hold doctorates in a relevant biological science. To achieve a measurable downregulation of protein expression, one need only contact the target cells with an adequate amount of antisense oligonucleotides. The infusion techniques are conventional and were fully known in 1981. The technique is merely the injection of a saline solution containing the antisense oligonucleotides into the appropriate organ. There is simply no basis to conclude that such an experimental step was anything but routine and intuitively apparent to those of skill.

The Examiner stated in Paper 35, that the specification failed to teach how to use the specific analogs. While there may be no express teaching of specific analogs other than the phosphotriesters, the specification generally teaches that protected and unprotected oligonucleotides can be used. Beyond specifying an

adequate length, there is no other teaching needed to practice the invention. The technology is just too simple. In appellant's response mailed July 20, 1995, th Examiner was asked to provide objective statements as to why he believed there to be some nonobvious complexity to this invention, which was not apparent to the appellant. The record is still silent as to any putative complexity.

Thirdly and finally, appellant believes that the Examiner's actual concern is not with "how to use" but with "which analog to use." The underlying question being raised is whether it would require undue experimentation to **select** working embodiments from among the universe of stabilized nucleic acids. Appellant responds by stating that **all the conventional analogs would work.**

Beyond internalization and hybridization concerns, there are no objective reasons to believe that the prior art nucleic acid analogs would not work to some degree to downregulate protein, provided an appropriate length was used. Both of these two concerns are addressed below in sections three and four respectively.

Reserving for the moment, a substantive rebuttal to internalization and hybridization concerns, appellant would like to address the Examiner's general concern over "which" stabilized nucleic acids would work. Drs. Schwartz and Ruth have identified five prior art references that describe stabilized nucleic acids (See the Communication mailed on April 14, 1995 at pages 4-5). All of the analogs described by the references have been altered to stabilize them against degradation by nucleases. They all have been chemically modified to stabilize them while preserving their ability to bind to complementary strands of nucleic acid. The field of pursuit represented by the five references describing different analogs is clearly focused on *maintaining* hybridization specificity while increasing stability against nuclease activity. In summary, there is no issue regarding which stabilized analog to choose. **They should all work in the invention!**

While appellant acknowledges and fully addresses below the only two colorable concerns raised by the Examiner. These reasons were raised in Office Actions dated years before the submission of the Rule 132 Declarations of Drs.

Schwartz and Ruth. In the declarations, the experts fully rebutted with objective reasons why the Examiner's two concerns were ill taken. The Examiner has not substantively responded to the declarations by articulating any objective, scientific reasons to cast doubt upon the truth of the experts' statements. There has been no explanation by the Examiner as to why he continues to believe that with knowledge of the effective prior art relating to stabilized nucleic acid, one of skill would undertake undue experimentation to identify stabilized nucleic acids able to selectively downregulate the expression of protein.

In view of the declarations by the two experts, the strength of the arguments set forth above and in the record, the issuance of U.S. Patent No. 5,023,243, and the lack of objective evidence to the contrary, appellant asks that Board reverse the Examiner over this second basis for rejection under §112, i.e., relating to a failure of the specification to teach how to use the nucleic acids.

3. THE SPECIFICATION NEED NOT SET FORTH AN EXPRESS STATEMENT REGARDING WHICH STABILIZED OLIGONUCLEOTIDES WILL ENTER CELLS BECAUSE THEY *ALL* ARE TAKEN UP BY CELLS.

As discussed above in Section 2, the Examiner initially raised colorable concerns regarding enablement that needed to be addressed by appellant. In the Office Action dated December 16, 1992, the Examiner was concerned that it would require undue experimentation to determine which of the available stabilized nucleic acids would enter a cell. Appellant believed that this basis for rejection was withdrawn in view of the appellant's comments and those of the declarants in the papers submitted on August 29, 1994. However, the Examiner broadly referred to his December 16, 1992 comments in his Advisory Action dated May 4, 1995 (paper No. 35) and for this reason, appellant is compelled to revisit the issue.

In appellant's communication dated August 19, 1994 in the paragraph bridging pages 6-7, and in the attached declarations of Drs. Schwartz and Ruth at section (5)(C), the issue of cellular uptake was addressed and fully traversed. In particular, the Examiner had raised a concern regarding the ability of cells to internalize nucleic acid. He commented that the specification provided no data and

methods for actually "getting short DNAs or RNAs into cells." In response, the appellant and declarants explained that normal living cells are quite amenable to internalizing short nucleic acid - both natural and stabilized nucleic acid. There is nothing to teach. Normal cells naturally internalize nucleic acids and this was known in 1981.

With regard to internalization of stabilized nucleic acid, the very literature relied upon by the Examiner to support his obviousness rejection teaches that short stabilized nucleic acids are internalized by cells. For example, the 1977 and 1981 Miller references (A1 and A2) describe the ability of two different small nucleic acid analogs to be internalized by mammalian cells. The 1978 Summerton reference (A28) disclosed at pages 93-94 the routine uptake by animal cells of both RNA and DNA. Indeed in the five references cited by the declarants as evidence of the availability of stabilized oligonucleotides in 1981, four of the five references report that their stabilized oligonucleotides are internalized by cells.[1]

The Examiner has not provided an adequate rebuttal in response to this overwhelming evidence - objective evidence from the literature and by the declarants that cellular uptake of natural and stabilized nucleic acid is neither unexpected nor unpredictable. Other than the totally subjective expression of concern by the Examiner, the record is devoid of any objective evidence. The Examiner has failed to either cite publications teaching the inability of cells to uptake nucleic acid or explain by sound scientific reasoning why the nature of cellular uptake of nucleic acid is so unpredictable that there would be undue experimentation regarding the internalization of the nucleic acid by the cells. In view of the lack of a cogent rebuttal, the Board is requested to reverse the Examiner on this third issue relating to the nature of cellular uptake of nucleic acid.

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[1] The Miller 1977 (A1) reference entitled, "Effects of a Trinucleotide Ethyl Phosphotriester, $G^mp(Et)G^mp(ET)U$, on Mammalian Cells in Culture," describes a 1974 reference (A9) in which the triester forms were synthesized.

4. BECAUSE STABILIZED NUCLEIC ACIDS ARE DESIGNED TO MIMIC NATURAL NUCLEIC ACID, THE SPECIFICATION ADEQUATELY ENABLES THE CLAIMED INVENTION WITHOUT EXPRESSLY SETTING FORTH WHICH OF THE CLASS OF STABILIZED NUCLEIC ACID WILL BIND TO THEIR TARGETS - *THEY ALL WILL BIND*.

Although appellant believes that this issue was previously traversed by argument, the Examiner has not expressly withdrawn this basis for rejection and, therefore appellant is compelled, as above in Section 3, to address this concern in the Brief. As appellant understands this concern, the Examiner in paper No. 26 at page 3, supports the §112 rejection with the following statement that:

> . . . none of the references discusses . . . (b) the ability of the particular oligodeoxyribonucleotides of any of the references to hybridize effectively to a nucleic acid of interest (i.e. a target nucleic acid)."

In many of the references that were relied upon by the Examiner to support the §103 rejection, the authors used modified, stabilized nucleic acids for binding to specific nucleic acid targets. These stabilized nucleic acids were chemically modified to mimic the natural properties of unstabilized nucleic acids while resisting degradation by nucleases. Based on these teachings, there is simply no scientific reason for the Examiner to presume that the stabilized nucleic acids available in 1981 would not have the ability to hybridize to complementary nucleic acid. They were designed to bind to target nucleic acid.

For example, Miller's work in 1977 (A1) with phosphonate analogs described the ability of these analogs to specifically bind intracellularly to initiation codons and tRNA binding sites of mRNA. The second sentence of reference A1 states:

> These neutral oligonucleotide analogues [phosphotriesters] were shown to be capable of forming specific, hydrogen-bonded complexes with complementary anticodon or 3'-amino acid accepting stem regions of transfer RNA at low temperature and ionic strength.

Similarly Miller in reference A2 states in the first column of the article:

> Extensive physical studies by ultraviolet, circular dichroism, and nuclear magnetic resonance spectroscopic techniques revealed that the conformation of these analogues [phosphonates] is similar to

> those of the corresponding phosphodiesters [natural nucleic acids] and that the analogues form stable complexes with complementary polynucleotides (Miller *et al.* 1977; Kan *et al.*, 1980).

The 1981 reference by Kunkel (Exhibit 1 of the April 14, 1995, declarations) details the use of their thiophosphate analogs as template for making DNA, and specifically acknowledges the base pairing specificity of the analogs during synthesis (see the bridging paragraph between pages 6735-6736 where the authors state:

> . . . the analogue is not mutagenic by any unexpected mechanisms, such as a change in base-pairing specificity.

This discussion of unchanged base-pair specificity is referring to complementary binding between bases of the analogs and natural DNA. If it is unchanged, there are no mutations.

Finally, the Summerton reference (A28) detailed the state of the art in 1978 with regard to the use of stabilized nucleic acid analogs as anticancer and antiviral agents. In the article, Dr. Summerton clearly states that analogs and derivatives of nucleic acids are functioning because of specific base pairing. He states at page 89:

> . . . there are a growing number of reports on antiviral and/or anticancer activity of homopolyribonucleotides, analogs, and derivatives thereof, and a synthetic oligodeoxy-ribonucleotide. The general rationale for this work is that the introduction of such polymers into virally infected cells may lead to pairing between the introduced polymer and a specific viral structure of nucleotide sequence. Presumably such pairing would inhibit some critical function in the virus life cycle.

From the above literature, it should be clear to the Board that the stabilized analogs of the prior art in 1981 were designed to hybridize to natural nucleic acid. They are competent to hybridize to nucleic acid via complementary base pairing in a manner equivalent to hybridization between the natural, phosphodiester forms of nucleic acid. Indeed, most of the literature describing stabilized nucleic acids is focused on modifications to the phosphate backbones, or to limited methylation of specific bases. These modifications are quite deliberately chosen to avoid physical

interference with complementary binding between bases. If one were to modify the nucleotide bases to the degree that specific hybridization was no longer possible, the bases would no longer be nucleic acid analogs -- they would be biologically inactive. No one of skill would attempt to study the biological properties of such an "analog". It would have no biological effect except perhaps as a food source.

The Examiner has not provided any substantive rebuttal to the above record despite an express invitation to do so. The present record is totally devoid of any objective reason as to why the Examiner continues to be concerned, if he actually does continue to believe, that the stabilized nucleic acids embraced by the claims would have an unpredictable ability to bind to their targets.

Although it might not be clear that the Examiner truly is concerned with the hybridization properties of stabilized nucleic acid, the law is clear with regard to the adequacy of the rebuttal by appellant. Furthermore, it is clearly not legally proper for an examiner to inquire of an issue, elicit a response based upon sound scientific reasons from the patent applicant, and then summarily dismiss the statements of the literature and experts without objective rebuttal reasons. In view of the above remarks, and the record as a whole, appellant believes that the Examiner's concerns have been fully addressed and that this fourth basis for supporting the §112 rejection be reversed.

5. WHILE STABILIZED NUCLEIC ACIDS ARE PREFERRED, THEY ARE NOT A REQUIREMENT FOR OPERABILITY AND THEREFORE THE EXAMINER HAS IMPROPERLY REJECTED THOSE CLAIMS EMBRACING NATURAL NUCLEIC ACIDS AS NON-ENABLED DUE TO A LACK OF STABILITY.

The Examiner has continuously maintained that stability of the nucleic acids is required for operability. He rejects claims that read on "natural" nucleic acids as overly broad because "natural" nucleic acids are subject to degradation by nucleases. The Examiner in the final Office Action mailed on November 28, 1994 states: "The arguments and declarations do not address the issue of stability of the oligodeoxyribonucleic acids in vivo." In brief, the Examiner is concerned that

unstabilized nucleic acid would be "cleaved" before it could bind to its target mRNA and downregulate the expression of protein.

Although the Examiner refers to this basis for the rejection as a pure enablement rejection under §112, it is obviously a hybrid §§101/112 rejection as discussed in *In re Ziegler*, 26 USPQ 1601 (Fed Cir 1993). According to *Ziegler*, if an Examiner has objective reasons to believe an invention does not work, the rejection can be under §101, §112 or both. No matter which statutory section is relied upon, the legal standards for establishing the rejection as well as the applicant's rebuttal are the same. *In re Brana*, 34 USPQ 2d 1436. (Fed. Cir. 1995) See also *Ex parte Aggarwal*, 23 USPQ 2d 1334 at 1337 (BPA&I 1992) where the Board faced with a hybrid rejection under §101 and §112 treated the dual rejection "as one rejection."

In response to the Examiner's concern over stability of natural nucleic acids, the appellant provided "later state of the art" references that confirmed that natural (unstabilized) nucleic acid could effectively downregulate protein expression but that due to nuclease activity it was not a preferred embodiment. In response, the Examiner in paper No. 35, states:

> Applicant's arguments in connection with utility are superfluous at best, but are given no weight at all whatsoever in connection with the rejection under 35 U.S.C. §112, first paragraph. Applicant additionally argues (page 11) that several references support the notion that intact oligonucleotides can be delivered to animals and isolated cells. This argument is not convincing because each of the articles was published subsequent to the effective filing date of the instant application.

The Examiner concludes by asserting that the appellant is estopped from obtaining claims to unstabilized nucleic acids by a statement made in 1984 to the effect that stabilized nucleic acids are preferred. In response, appellant will address each of the above issues in turn.

A. The PTO must consider extrinsic evidence when submitted to establish that a challenged statement of utility is true regardless of whether the rejection is made under §101 or §112.

The Examiner takes the legally unsupportable position that because he questions the utility of the invention under §112, he is free of the burden of considering post filing date proofs of operability. In the *Brana* decision, the Federal Circuit expressly analyzed a utility rejection under §112 because the Board had expressly done so. However, the case law relied upon by the court was the very same case law that recognized the intertwining nature of §101 and §112 and the legal reasoning articulated by the court was essentially the same as used by the Board and the courts when addressing breadth issues independently under either §101 or §112.

In brief, the PTO has the initial burden to come forward with objective reasons to doubt the utility and the patent applicant must convince the PTO that the utility is reasonable by scientific evidence. While not addressed in *Brana*, the case law is clear that it is appropriate to rebut a question of utility by post filing date or extrinsic evidence.

Publications that are available after an effective filing date are termed "later state of the art." A seminal case defining the proper use of later state of the art references is *In re Hogan and Banks*, 194 USPQ 527, 537 (CCPA 1977). In reversing a PTO rejection, the CCPA had opportunity to discuss the proper use of later state of the art references. The CCPA summarized the various decisions that approved the use of later state of the art to establish: (1) that undue experimentation was required or not required, (2) that an alleged utility was or was not true, (3) that a statement in the specification was or was not accurate, or (4) that a parameter absent from the claims was or was not critical. In contrast to the Examiner's view, the statutory section itself is not determinative of the proper use of later state of the art references.

The pending rejection under §112 can be viewed as either (1) questioning the objective truth of the stated scope of utility or (2) concerning whether or not

the parameter of "stabilized oligonucleotides" is critical to utility. Accordingly, it is clearly beyond the authority of a patent examiner to refuse to consider later state of the art references when they are submitted for the purpose of establishing that the invention works as claimed or that a specific element is not critical to the successful function of an invention.

In the instant situation, the references described below and the statements by the declarants are submitted as evidence of the truth of the fact that unmodified oligonucleotides will function, as claimed, to downregulate protein expression under *in vivo* conditions. Appellant is not relying on these references for the disclosure of facts that were required to practice the invention and that were unavailable in 1981 when the application was filed. The references were submitted solely to establish the objective truth of the *in vivo* utility of unmodified oligonucleotides. Thus, it is entirely proper for the Examiner to consider the references as a rebuttal to his concerns regarding scope of utility under §112.

Two cases illustrate the use of "later state of the art" teachings or affidavits to rebut a utility rejection. They are *In re Irons*, 144 USPQ 351 (CCPA 1965) and *Aggarwal*, 23 USPQ 2d 1334 (1992). In *Aggarwal*, this Board substantively evaluated the Sherwin declaration in regard to rebutting a hybrid §101/§112 rejection. Following *Irons* and this Board's own precedent, the Examiner's refusal to substantively evaluate the post filing date references should be reversed and the references substantively considered.

B. The evidentiary record is replete with references that teach that unstabilized nucleic acid will have utility in this invention; and therefore the statements of the specification that natural nucleic acid will downregulate protein expression are legally sufficient to support the pending claims.

Having explained above that the Examiner's refusal to substantively consider later state of the art references is improper, appellant will summarize the substance of the references in this subsection. A total of six references (exhibits 3-9) were submitted as exhibits and summarized in accompanying Rule 132 declarations by Drs. Schwartz and Ruth, filed on April 14, 1995. Of the six references,

Exhibits 7-9 were uncontroverted on their facts regarding operability of the claimed invention. Each of the following points was expressly presented to the Examiner.

In exhibits 3 and 4, Michelson *et al.* and Wolff *et al.* respectively, it was explained that nucleic acid can survive for long periods under *in vivo* conditions despite endogenous nuclease activity. Michelson *et al.* reported that ribonucleic acid survives up to a week inside the body of a rabbit. The article further indicates that the selected ribonucleic acid is biologically active for controlling neoplasms. The authors reported that no special delivery system was required to deliver either purified RNA or DNA and to permit its internalization by cells and subsequent expression (see Abstract). They further reported that three different genes were expressed by the mice. In Wolff *et al.* the authors described the expression of RNA after it was directly injected into the muscle tissue of a mouse.

The appellant notes that in paper No. 35, the Examiner criticized exhibits 3 and 4 for not specifically using single stranded nucleic acid. While this is true, the extra and intracellular environments of concern to the Examiner comprise nucleases that can cleave both single and double stranded nucleic acid. Appellant was merely providing evidence that unstabilized nucleic acid in general was more stable than the Examiner might have understood from his personal knowledge. Furthermore this criticism is rendered moot in view of exhibits 7, 8 and 9, which are references that disclose the survival of single stranded nucleic acids under *in vivo* conditions and specifically address the Examiner's concern.

In addition to exhibits 3 and 4, appellant provided exhibits 5 and 6 which reported on the injection of unmodified, natural DNA directly into animals and reported the expression of the genes. In exhibit 5, Lin *et al.* (1990), the authors report on the expression of recombinant genes in heart tissue after the genes are simply injected into the heart of a living rat. The transfer media was simply phosphate buffered saline and sucrose. In exhibit 6, Wolff *et al.* (1992), a second group reported similar results in mouse skeletal muscle using a gene encoding luciferase, and on page 368 (second column), the authors report on analogous

results in a primate heart. These references were provided to explain that both linear and circular DNA are equally biologically active under *in vivo* conditions.

Again the Examiner finds substantive fault with these references because they used double stranded nucleic acid rather than single stranded nucleic acid. Of course, the appellant was merely establishing further evidence of the survivability of nucleic acid under *in vivo* conditions where nuclease activity is presumed present.

Finally and most significantly, the appellant presented three references in which unmodified antisense oligonucleotides were used as single stranded agents. The references report that the agents downregulated specific gene expression in a variety of different tissues. In exhibit 7, Phillips *et al.* (1994) the authors report on the successful downregulation of angiotensin and the AT_1 receptor by directly injecting an unmodified antisense DNA for reducing hypertension in mice. The DNA was merely injected into the mouse carotid artery using a saline solution. In exhibit 8, Akabayashi *et al.* (1994), the authors added DNA to a saline solution and simply injected the solution into the brain to inhibit the expression of a neuropeptide. At page 56, first column, the authors state that theirs is the third report describing downregulation of protein expression. Finally, in exhibit 9, Hijiya *et al.* (1994), the authors report on the use of an unmodified phosphodiester oligonucleotide for controlling the expression of a gene which is involved in skin cancer. The authors applied the antisense oligonucleotide via a subcutaneous route and used constant-infusion pumps to ensure that the oligonucleotide was adequately administered.

The examiner had no substantive criticism of exhibits 7-9 except to remark that he would not consider them substantively because they are post filing references.

In view of the legal arguments in Section 5A addressing the propriety of the submission of post filing date references and the actual teachings of those references, it is submitted that the Examiner's concerns about utility of the

invention under §112, first paragraph, are fully addressed and the rejection of the claims over this fifth basis should be reversed.

C. Appellant should not be irrebuttably estopped from pursuing claims directed to unstabilized nucleic acid by a poorly phrased statement in the record.

In support of the §112 rejection, the Examiner relied upon a statement in a Disclosure Statement filed by appellant's previous attorney on February 1, 1984 in related application, USSN 06/314,124. The statement was made in the context of disclosing publications by Zamecnik and Stephenson. In accordance with the practice at the time, the appellant described the relevance of the publications to the pending claims. At that time, the appellant's pending claims were limited to stabilized oligonucleotides (i.e. claim 71), and appellant's attorney stated: "Finally, Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect."

The Examiner interprets this statement as an *irrebuttable* admission that unmodified DNA could not be used in the invention. Appellant respectfully submits that the Examiner has read too much into this statement. The statement was made in the context of distinguishing the pending claims over prior art. Three points of distinction were presented on pages 2-3 of the Disclosure Statement. The first two points noted that the prior art of Zamecnik and Stephenson targeted *non-coding* regions of the mRNA of a virus and that the reported reduction in viral replication was thought to be due to inhibition of circularization of the viral nucleic acids and not necessarily due to inhibition of protein expression. As a final point of distinction, the appellant noted that the prior art workers used unprotected nucleic acid which, unlike the claims pending at the time, were subject to degradation under *in vivo* conditions.

The Examiner would have this Board interpret the above sentence as an irrebuttable admission that unprotected nucleic acids lack utility. This interpretation ignores the context in which the sentence was actually used by the appellant. The sentence at issue was made in the context of traversing a possible §102 and §103

rejection. It was made as a final point of distinction and the status of the current claims embracing both unprotected and protected nucleic acids makes it clear that this third argument was not controlling of novelty or obviousness.

By relying upon this sentence as support for the current §112 rejection, the Examiner asks the Board to ignore the different requirements between the relevant statutory sections. When analyzing the significance of prior art under sections 102 and 103, the PTO properly considers, weighs and balances issues of degree and combinations of factual points. In contrast, a rejection under §112 for non-working embodiments requires the PTO to establish that the embodiments do not work at all. There is no balancing of facts. Utility is a function of purpose and not a subjective measure of quality or degree. An invention need not work well, it need only function. *In re Ruskin*, 148 USPQ 221 (CCPA, 1966) at 222 and *In re Barmony Barmer Maschinenfabrik AG v. Murata Machinery Ltd.*, 221 USPQ 561 at 563 (Fed. Cir. 1984). Moreover, the recited utility need not be a commercially practical utility. *Ex parte McKay*, 200 USPQ 324 (PTO BD APP 1978), where the Patent Office Board of Appeal reversed a utility rejection for a process which was limited to use on the moon.

The sentence at issue does not state that the unprotected nucleic acids *are totally unable* to control cell expression. The sentence just states that they will break down under *in vivo* conditions before having the desired effect. They do break down. But, this fact is not a failure of purpose. First, under some conditions, such as *ex vivo*, the invention works well regardless of the stability of the nucleic acids. Second, under conditions where degradation is a problem, one can easily accommodate for the presence of degradation by applying greater amounts of the nucleic acid. According to the declarants' April 14, 1995 statements in the final paragraph of section C , degradation of unprotected nucleic acid is routinely solved by simply increasing the amount of nucleic acid applied to target cells.

Notwithstanding the fact that protected nucleic acids are preferred for most applications, the appellant should not be limited in his claim scope simply because he expresses a rationale for his preference. There is no factual evidence before this Board that unprotected nucleic acid will not work. In summary, unprotected nucleic acid may not be commercially feasible for some applications, but so long as it works for a single application embraced by the appealed claims, they meet the requirements of §112.

Even presuming that the sentence at issue properly raises a question regarding the utility of unmodified, phosphodiester oligodeoxyribonucleotides under *in vivo* conditions, the sentence is far from an irrebuttable admission of a lack of utility. The Examiner's interpretation of the statement as an admission is clearly not the only possible interpretation of the sentence. Moreover, even if the statement were unambiguous, a poorly worded sentence should not be viewed as an error fatal to patentability while prosecution is ongoing.

Ambiguous and incorrect statements are occasionally made by patent applicants during prosecution. Basic elements of fairness should be considered and the appellant should not be precluded from retracting misstatements or explaining an apparent ambiguity in statements made during prosecution.

Ironically, when the above remarks were first presented to the Examiner in the papers filed on April 28, 1995, the Examiner responded in paper No. 35 by relying upon a 1992 reference written by appellant. Apparently, the Examiner had no difficulty using extrinsic evidence when it purported to support his position; but he refused to consider extrinsic evidence when it did not support his position.

Of course the use of post filing date references is appropriate under both circumstances. Appellant has reviewed the final reference. In short, the Examiner has patently misconstrued the plain meaning of the 1992 abstract.

The title of the 1992 article by appellant Dr. Tullis, is "Antisense Applications of Synthetic Nucleic acids." The focus of the article is to explain that chemically synthesized nucleic acids have been a key development towards

commercialization of the therapeutic applications of the technology claimed in the 1981 application of Tullis. This was in contrast to unmodified nucleic acids that are created by biological processes.

The Examiner has focused on the last two sentences of the abstract which states:

> While the diagnostic applications of nucleic acid hybridization probes are already well developed, therapeutic applications have been largely ignored. In the past few years, the development of synthetic methods to produce DNAs containing a variety of structural modifications have made DNA therapeutics feasible.

The Examiner would have the Board read this statement out of context and interpret the word "feasible" as meaning "possible" rather than "commercially valuable". However in context, it is clear that the authors are describing a situation where the therapeutic applications are merely more practical today than in early days.

The Board's attention is directed to the following passages in the article. On page 79, last paragraph of the second column, the authors describe the two basic approaches for creating the antisense molecules by biological and synthetic m ans. The first paragraph on page 80 explains that both approaches have been successful and then explains that synthetic chemistries have brought the technology to the forefront of the "commercial application." The authors go on to bullet point in the very next paragraph the importance of commercial scale production by the use of synthetic chemistry.

The Board is also asked to take note of the examples chosen by Dr. Tullis to illustrate synthetic, stabilized oligonucleotides - especially at page 81, the last sentence of the first column. The authors state that both methylphosphonates, which was a part of the prior art in 1981 (See reference A2), and alkylphosphotriesters, which are the specific analogs described in the appellant's application, have been successfully used. Because both analogs were available prior to 1981, the Examiner's interpretation of this reference as proof that the pending claims were not enabled in 1981 becomes untenable.

Furthermore, the Board should take note that the 1992 reference speaks only to therapeutic applications. In contrast the pending claims are broader than that single specific application. The fact that the Examiner has concerns over a single utility is simply not relevant to method claims that have alternative utilities, i.e. downregulating proteins under research conditions or under industrial applications such as fermentation processes.

Having explained the appellant's actual intent of the sentence at issue, the Board is asked to reverse the Examiner with regard to any estoppel raised by the statements in 1984. In subsection 2 above, it was explained that although oligo-DNAs may be unstable over a long period of time, the degree of stability does not prevent the practice of the invention *in vivo*. This logic has been consistently maintained by the appellant throughout prosecution and to maintain this rejection over the subject sentence is to unfairly limit the appellant's claims to stabilized nucleic acid. The use of stabilized nucleic acid is merely a preferred embodiment and for the above reasons, the Examiner's rejection of the pending claims for failing to be enabled beyond stabilized nucleic acid should be reversed.

6. THERE IS NO UNDUE EXPERIMENTATION REQUIRED TO PRACTICE THIS INVENTION.

In Section 5, appellant urges that the Examiner's reasoning in support of his enablement rejection due to a lack of stability is fallacious because in fact natural nucleic acids are stable and operable as stated in the specification. Appellant's previous response focuses upon the issues raised by a *hybrid* rejection under §101 and §112. For completeness, appellant would like to address the rejection from a classic enablement perspective. Appellant would like to briefly explain that it would not require undue experimentation to reduce this invention to practice.

As set forth above, the heart of the invention is the targeting of the coding region of the mRNA with target-specific nucleic acid of an appropriate length. Once the inventive aspects of the oligonucleotides are recited, the physical practice of the invention is trivial. Given the level of skill in this art, the use of the

invention to downregulate protein expression under *in vivo* conditions does not require undue experimentation.

More specifically, appellant submits that the physical practice of the invention does not require any particular complexity or unpredictable effort and thus no undue experimentation is required when practicing of the invention. The Board is asked to take note of section D of Drs. Schwartz and Ruth declarations dated April 14, 1995. Section D addresses the question of undue experimentation with regard to the practice of the claimed invention.

The practice of the invention merely asks one of skill to contact target tissue in a physiologically compatible buffer containing the oligonucleotides. It is an obvious extension of the protocols using cells *in vitro* that are expressly taught by the specification. The issuance of U.S. 5,023,243 is evidence that the Examiner does not find concern with the physical aspects of the working of the invention. His sole remaining concern relates to the selection of the analogs and the utility of unstabilized nucleic acid.

7. THE EXAMINER HAS IGNORED THE TRUE INVENTIVE PRINCIPLE OF THE CLAIMED INVENTION AND UNDULY FOCUSED ON A NON-INVENTIVE FEATURE OF THE INVENTION.

In the above discussion, the appellant addressed the enablement rejection from the perspective of whether the initial evidentiary burdens have been met by the PTO. Appellant then explained that his substantive rebuttal provided objective, scientific reasons why the claims are fully enabled. In this final section, appellant asks the Board to view the rejection from a purely legal perspective. As explained in more detail below, the Examiner's enablement rejection is focused on a trivial aspect of the invention and as such, the rejection should be reversed as not controlling of patentability.

In short, the invention is directed to any nucleic acids that bind to the coding region of mRNA to selectively inhibit expression of the protein encoded by that mRNA. The type of nucleic acid used to bind to the mRNA is irrelevant! The key

concept of the invention has been deemed nonobvious and the remaining issue over the "type" of nucleic acid should not be controlling of patentability.

In 1981, there were several stabilized nucleic acids available for use. In 1995, there are more stabilized nucleic acids available for use in the invention than in 1981, and in 2005 there will be even more stabilized forms of nucleic acid available than in 1995. The broadest claims do not claim property rights to any specific stabilized nucleic acid and patentability should not hinge on a recitation of specific nucleic acid analogs available in 1981.

There is clear decisional law that enablement concerns for method claims, of the type now pending, must be confined to the patentable or inventive principles of the claimed method. Appellant asks the Board to consider three controlling CCPA opinions that provide guidance with regard to the scope of enablement as it relat s to the inventive principles of a claimed method.

In *Application of Fuetterer*, 138 USPQ 217 (CCPA 1963), the applicant had discovered that by combining a protein with an inorganic salt to the materials used to make tire tread, one could increase the stopping ability of tires made from the materials. The Examiner in *Fuetterer* argued that the scope of the claims was too broad and the amount of experimentation required to successfully use undisclosed inorganic salts should require the applicant to restrict his claims to the disclosed salts. The CCPA reversed the breadth rejection, explaining that this invention was the combination of inorganic salts with the other elements of the claims. The fact that novel inorganic salts might be later developed did not preclude broad claims to the inventive combination.

Fuetterer was followed by *Application of Herschler*, 200 USPQ 711 (CCPA 1979). In *Herschler*, the applicant had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing a single steroid (dexamethasone 21-phosphate) adequately supported a claim to the genus of all steroids. Citing *Fuetterer*, the court explained that *Herschler*'s claims were not drawn to a novel

steroid but to a method for the administration of steroids. As long as the class of steroids was reasonably expected to be transported across the skin by DMSO, the claim could encompass any steroid, known or unknown. As in *Fuetterer*, the CCPA reminded the Patent Office that the inventive principle was directed to a method of administration of steroids and that the specific steroid exemplified was not the point of patentability.

Herschler explains that the proper focus of a breadth rejection under §112 should be on the inventive features of the claim and not on the non-inventive features. There the court stated:

> The solicitor urges that the class of steroids is so large that a single example in the specification could not describe the varied members with their further varied properties. We disagree with this contention. Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, *when considered as a class of compounds carried through a layer of skin by DMSO*, appear on this record to be chemically quite similar. (*Herschler* at 717; Italics added)

The invention in *Herschler* concerns the transdermal transport of steroids by DMSO; accordingly, steroids are considered as a class of compounds carried through skin and found to be presumptively similar in their ability to be carried.

A third case on point is *In re Lange*, 209 USPQ 288 (CCPA 1981). In *Lange*, the CCPA considered whether claims to a circuit breaker with electrodes consisting of a physical combination of metallic materials and non-metallic gas-emitting compounds were enabled by a grandparent application. The grandparent application did not teach how these materials could be cast together to form electrodes; but it did teach how metallic materials and non-metallic gas-emitting compounds could be superimposed in layers. The CCPA found that the grandparent application was sufficient to enable claims directed to intimate mixing of the materials and compounds because the inventive principle did not reside in the *preparation* of electrodes but in the *use* of the electronegative nonmetallic gases. The court stated: "the method of forming the electrodes is not the inventive principle."

Fuetterer, *Herschler* and *Lange* illuminate the instant situation. In the instant invention, the discovery, synthesis or characterization of oligonucleotide analogues is not an inventive principle of the claims. Appellant is only required to enable the claimed *method of using* oligonucleotides, and has done so by specifying: (1) that the oligonucleotides are complementary to the mRNA coding region and thus they can bind the coding region of a target mRNA; (2) that the nucleic acids are preferably about 14 to 23 bases in length; and, (3) that the nucleic acids are preferably stabilized. As noted above, once provided with this guidance, one of skill requires no undue experimentation to identify other working oligonucleotides and practice the claimed method.

In accord with the case law, appellant emphasizes that he does not claim the rights to specific phosphodiester oligodeoxyribonucleotides, phosphotriester oligodeoxyribonucleotides, or any other compositions of matter. Thus, like Herschler, who discovered that DMSO carries steroids, as a general class, across the skin and sought claims that were not limited to specific steroid compositions, appellant has taught that nucleic acids as a general class, can access the coding region of mRNA and can inhibit specific protein expression. In view of this teaching, appellant seeks patent protection for claims not limited to a particular sequence or a particular modification of nucleic acid and asks the Board to reverse the Examiner on this final basis for maintaining the §112 rejection.

CONCLUSION

Appellant has presented multiple reasons why the single remaining rejection should be reversed. By law, a proper *prima facie* case of non-enablement requires that the PTO meet a minimum burden of establishing by a preponderance of the evidence that the practice of the claimed invention requires undue experimentation. Herein the appellant has forcefully argued that the *prima facie* case was not properly supported by objective reasons as to claim 71 relating to stabilized nucleic acids and that most if not all of the "objective reasons" raised by the Examiner

with regard to the other pending claims were "subjective" concerns that did not have any objective basis, i.e. scientific reasoning to support them. Furthermore where the Examiner did raise a colorable concern, especially with regard to the utility of stabilized nucleic acid, the appellant painstakingly addressed each concern posited by the Examiner and had two experts in the field lay them to rest with sound scientific reasoning. In view of the record, appellant submits that at a minimum, the issue of enablement has been placed into equipoise if not beyond.

In view of the above remarks, the declarations of the two experts and the record as a whole, appellant asks that the Examiner's rejection of the pending claims under §112, first paragraph, be reversed.

Respectfully submitted,

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APPENDIX

64. A method of selectively inhibiting the expression of a target protein in a cell producing messenger ribonucleic acids encoding the target protein and other proteins without inhibiting the expression of the other proteins, said method comprising the steps of:

(a) synthesizing an oligonucleotide having a base sequence substantially complementary to a subsequence of a messenger ribonucleic acid said subsequence coding for the target protein,

(b) introducing the oligonucleotide into the cell; and,

(c) hybridizing the oligonucleotide to the subsequence of the messenger ribonucleic acid to inhibit the expression of the target protein.

65. A method of claim 64 wherein the entire sequence of the oligonucleotide is complementary to the subsequence of a messenger ribonucleic acid coding for the target protein.

66. A method of claim 64 wherein the oligonucleotide is at least 14 bases in length.

67. A method of claim 64 wherein the oligonucleotide is about 23 bases in length.

68. A method of claim 64 wherein the oligonucleotide is between 14 and 23 bases in length.

69. A method of claim 64 wherein the messenger ribonucleic acid is viral.

70. A method of claim 64 wherein the messenger ribonucleic acid encodes a hormone.

71. A method of claim 64 wherein the oligonucleotide is stabilized to inhibit degradation by nucleases.

72. A method of claim 64 wherein the oligonucleotide is a oligodeoxynucleotide.

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